



**White Paper on
Managing product benefit-risk in a challenging environment**

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Times have rarely been more challenging in the world of drug safety. The pharmaceutical industry and its Regulators are under pressure to improve the benefit-risk profiles of therapeutics, as further high profile safety issues become apparent. The increased Regulatory emphasis on improving the balance of benefit to risk is clear, and recent Regulatory interventions have been dramatic. The FDA requirement for safety-related label updates on GSK's Advair/Seretide provide a very recent example. The commercial consequences of this environment are huge, and not just for the company directly involved. The fall-out from Vioxx hit Pfizer almost as hard as Merck.

This brief paper argues that holistic risk management interventions need to be initiated and tracked using improved evidence from healthcare data systems.

An old chestnut

Since the days of "quack" physicians operating as salesmen of their own drugs, the safety of therapeutics has been called into question. Around the world, physicians in training are now routinely reminded that no drug is safe. Indeed, several drugs marketed and routinely administered for years would today fail to gain a marketing authorisation for safety reasons.

Since the inception of modern drug regulation, drug safety assessments have been increasingly formalised. The safety of many drugs have been called into question and ultimately withdrawn. Few major companies have escaped unscathed. Seasoned industry observers cite a long list of affected products since the 1962 Kefauver-Harris drug amendments to the Food and Drugs Act sparked by the Thalidomide disaster. Seldane, Propulsid, Redux, Lotronex, Baycol, Posicor, Rezulin and of course Vioxx are well known examples.

As the industry comes under increasing commercial pressure, exacerbated by a relative dearth of innovation in the last 20 years, the contribution to population risk of aggressive marketing and sales practices has been scrutinised. Many argue that the shift in emphasis of the industry towards "lifestyle conditions", the proliferation of line extensions to drive sales, an increase in both overt and covert direct-to-consumer advertising and the salesforce "arms race" have further increased Regulators' sensitivity to product risk.

How effective is risk management today?

Arguably, not very. The Vioxx case has called into question the probity and transparency of both the marketing authorisation holder and the FDA. It seems clear that decision-making was based on narrowly-defined, and relatively small clinical trials. Despite early signals, the resulting interventions were limited and ineffective. The detrimental outcome was a result of actions being taken "too little, too late". Accusations that inadequate data were made available for evaluation, and then evaluated with insufficient rigour, are laid at the door of both Merck & Co and the FDA.

Of course, Vioxx is not the only and possibly not the best example of these issues. Take Propulsid, which was available on prescription between 1993 and 2000. Five times between its approval in 1993 and withdrawal in January, 2000, the labelling for the drug was tightened, resulting from increasing concerns about potential arrhythmias and risk of sudden death. The FDA's initial position was that the risk seemed "very low" but as further evidence accumulated it became clear that most deaths from Propulsid occurred in patients that were specifically contra-indicated.

In 1998, the UK Medicines Control Agency (now MHRA) blocked use of Propulsid in infants and cautioned against prescribing it to children up to age 12. The agency commented "Restricted-access schemes are not adequate to protect public health". Other European regulators took a less interventionist stance.

J&J commented "that despite the warnings, some inappropriate use has continued in the United States." The best solution, the company said "was limiting access to the drug, whilst ensuring that appropriate patients who have exhausted other treatment options can still benefit from it." The product still had to be withdrawn.

Lotronex provides another example of where product labelling provided insufficient control on the use of the drug. The drug was thought to have clear benefits in users with diarrhoea-predominant Irritable Bowel Syndrome, but was considered to risk severe toxicity in patients with the constipation-predominant form of the syndrome. The label communicated this but still the product was mis-prescribed and the product withdrawn soon after its approval in 2000.

Establishing a virtuous circle

Establishing a virtuous circle of improved evidence gathering combined with a better understanding of the impact of public health interventions is central to making progress in risk management.



Improved evidence gathering

The industry and its Regulators need to move away from a staple "safety diet" of small randomized controlled trials (RCTs) as the cost of these does not justify the value of the safety data they return. Post-marketing safety studies and registries have similar limitations.

The vastly increasing quantity and improving quality of observational healthcare data, and strategies in countries such as the US, UK and Netherlands of integration between care settings, allows for enormous potential for clinical data analysis. In the UK, the NHS IT Programme - Connecting for Health - aims to bring this potential to reality, although the support for pharmacoepidemiological and other health outcomes analyses appears a low priority.

The industry and its stakeholders should therefore work towards a future of near-unlimited observational data from integrated electronic health records. Alongside this main thrust of healthcare record integration, the government and industry should jointly sponsor greater academic focus on pharmacoepidemiology and healthcare providers should contribute more to understanding patients' comprehension of, and attitudes towards, product risk.

Impact of interventions

Interventions need to become much more wide-ranging than making incremental updates to the product's label. It is apparent that the approach to health care practitioner and patient information needs to be addressed to improve both information utility and access. Reasoned trade-offs need to be made between completeness and clarity. Plain English (or other languages as appropriate) is a must. Public health campaigns must be considered to address

specific high-importance product risks. These need to be informed by research into how best to communicate concepts of risk-benefit to patients, with active consultation of representative patient groups. An ability to assess the effectiveness of interventions is critical to ongoing improvement. In this regard the opportunity to assess outcomes from high-quality observational data sources becomes particularly valuable.

Implementation

Implementation in risk management is the primary issue of concern. No single party can unilaterally effect the changes required. Genuine co-operation between government agencies, healthcare providers, physician bodies and patient groups in setting strategy is required, as part of a long-term plan with near-term milestones to demonstrate useful progress.

Where to start?

While arguably an incremental step, the improvement of both the content and presentation of product information is a good place to start, focusing on the patient. In part this is recognized by the enactment of the recent amendment to EC Directive 2001/83/EC. It is now the Industry's turn to look at its product information and to redefine both the information made available to patients and health care practitioners, and how it is presented.

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- Performance management including performance scorecards and benchmarking
- Change and programme management
- Product, Market and Company research and analysis.



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